The roles of noncoding RNAs in B-cel lymphomas

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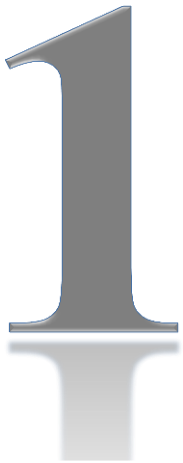
DOI:
10.33612/diss.134190556

Chapter 1

Introduction

and scope of the thesis



Introduction

1. B-cell lymphoma

B-cell lymphomas are a group of malignancies with distinct genetic and clinical features. Most lymphoma subtypes are derived from B cells at the germinal center (GC) stage of development. These GC-B cell derived lymphomas include amongst others Burkitt lymphoma (BL), Hodgkin lymphoma (HL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) [1-3]. Germinal centers (GC) are histological structures that are formed in lymph nodes when naive B-cells encounter antigens [4]. These so-called germinal center B-cells (GC-B) are divided into two distinct subtypes, i.e. centroblasts and centrocytes. Centroblasts are rapidly proliferating B cells located in the dark zone of the GC. These cells undergo somatic hypermutation (SHM) of the immunoglobulin (Ig) genes to enhance affinity of the B cell receptor (BCR) to the antigens. Centrocytes, located in the light zone of the GC, are GC-B cells selected based on expression of a high-affinity BCR [5]. Another process involved in B cell maturation is class switch recombination (CSR). CSR is an activation-induced cytidine deaminase (AID)-dependent recombination and deletion mechanism that juxtaposes a downstream Ig heavy chain segment to the rearranged segment, thereby switching the Ig isotype of a B cell [6,7]. B cells that produce high affinity BCR will be positively selected and mature into memory B cells and plasma cells, whereas B cells that do not produce functional or low affinity BCR will be eliminated by undergoing apoptosis. Both SHM and CSR are processes that can lead to accumulation of mutations and chromosomal breaks and allow GC-B cells to escape from apoptosis. This might explain the high incidence of lymphomas being derived from GC-B cells [2,8].

2. Burkitt lymphoma (BL)

In 1958, Dennis Burkitt described 38 cases of childhood lymphoma in Uganda and that was the first report of a disease that was later referred to as Burkitt lymphoma (BL) [9]. BL is one of the fastest growing human tumors, with a cell doubling time of about 24 hours, that mainly affects children and young adults [10]. The WHO classification distinguishes three BL subtypes: endemic BL (eBL), sporadic BL (sBL), and immunodeficiency-related BL [3]. eBL includes all cases from Africa and most of them are associated with Epstein-Barr virus (EBV). The annual incidence of eBL is about 40-50 per million children aged 3-12 years, with a peak at the age of 6 [11,12]. Jaw, periorbital swellings, or abdominal involvement are the most common sites of presentation [13]. In sBL, association with EBV is less common with a frequency of 10-20% [14]. The incidence of sBL is about 2 cases per million children and occurs more commonly in boys than in girls. The most common sites of sBL are abdomen

(60-80%), head, or neck [15]. The sBL makes up 1-2% of adult lymphomas and 30-40% of childhood non-Hodgkin lymphomas (NHLs) in Europe and north America [15]. Immunodeficiency-related BL has an annual incidence in the USA of about 22 per 100,000 AIDS-affected individuals [14,16]. This subtype constitutes 24%-35% of all HIV-related NHLs [17] and the common sites of presentation are both extranodal and nodal [18].

BL treatment consists of intensive chemotherapy using a combination of cyclophosphamide, prednisolone, and vincristine. The survival rate of eBL is relatively low, with a cure rate of 30%-50% [14]. This is mainly caused by incomplete treatment in low income areas [19]. The cure rate of sBL is roughly 90% [20]. For advanced-stage HIV-positive BL, the 2-year overall survival is about 50% [21]. In a more recent study, the survival rate of progressive or relapsed BL was improved significantly by treating with rituximab followed by blood stem cell transplantation [22]. Although the majority of patients respond well, serious therapy-related side effects are observed, such as hematological toxic effects, mucositis, or severe infections [19].

BL cells originate from germinal centers (GC)-B cells. Gene expression profiling of BL and normal B-cell subsets showed that the expression profile of BL cells most closely resemble that of centroblasts [14,23]. BL is characterized by monomorphic medium-sized cells, coarse chromatin nucleoli, and a high proliferation rate [24]. BL cells express the B-cell markers CD20 and CD79a.

In 1975, a chromosomal translocation t(8;14)(q24;q32), involving MYC and the Ig heavy chain gene locus, was discovered in BL [25]. Based on this and many subsequent studies, translocation of MYC to the Ig heavy or one of the light gene regions is regarded as the hallmark of BL. Gene expression profiling may help to diagnose BL, especially for cases with a morphology resembling diffuse large B-cell lymphoma [26].

As a result of the characteristic translocation, MYC is upregulated by juxtaposition of the Ig enhancer elements to the MYC gene. MYC is a transcription factor that binds to thousands of genomic loci and regulates expression of both protein coding and noncoding genes. As such, MYC is crucially involved in cellular processes such as cell proliferation, cell cycle, differentiation, and apoptosis [2]. Further support of the important role of MYC in the pathogenesis of BL was based on the development of B-cell malignancies in a mice model with ectopic MYC expression in the B-cell lineage. However the relative long latency period before lymphoma onset indicated that besides MYC overexpression, additional aberrations are required for a full malignant transformation of the B cells [27]. In other B-cell lymphoma subtypes, translocations involving the MYC locus are less common. More recently MYC was proved to be a general amplifier of actively transcribed genes [28]. In BL, MYC

regulated, next to an extensive set of protein coding genes, more than 50 miRNAs [29] and over 1,200 long noncoding RNA loci [30].

3. Hodgkin lymphoma (HL)

Hodgkin lymphoma (HL) was described as a unique entity by Thomas Hodgkin more than 180 years ago. Based on the morphology of the tumor cells and the composition of the cellular infiltrate, HL is classified into classical Hodgkin lymphoma (cHL), which accounts for about 95% cases, and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), which accounts for about 5% cases. Both cHL and NLPHL are characterized by a relatively low abundance (often ≤1%) of tumor cells. In cHL, the tumor cells are referred to as Hodgkin and Reed-Sternberg (HRS) cells which are characterized as large mono- or multi-nucleated cells [31]. Based on the presence of hypermutated immunoglobulin genes, HRS cells are thought to be derived from germinal center B-cells. Nonetheless, they often lack the expression of common B-cell markers [32-34]. HL accounts for 15% to 25% of all lymphomas [35] with an incidence of about 3 cases per 100,000 people per year. It is most common in young adults and in adults aged over 50 years. The cure rate of HL is roughly 80-90% upon current treatment protocols which involve multi-agent chemotherapy with or without radiotherapy [36].

4. MicroRNAs and long non-coding RNAs

Multiple studies have shown that protein-coding genes only make up less than 2% of the human genome. However, a major part of the genome is actively transcribed and these are referred to as noncoding RNAs [37,38]. These noncoding RNAs are classified into several subtypes, including microRNAs (miRNAs) and long noncoding (lnc)RNAs. A rapidly increasing number of studies show the importance of noncoding RNAs in almost all biological processes. In recent years, both miRNAs and lncRNAs have been studied extensively.

4.1 MicroRNAs

4.1.1 Biogenesis

MiRNAs are a group of 21-24nt noncoding RNAs that regulate gene expression at the post-transcriptional level [39]. The first miRNA, lin-4, was discovered more than 20 years ago in Caenorhabditis elegans [40]. Until now more than 2,800 mature miRNAs have been identified in human [41]. Most microRNAs are transcribed from the genome as longer primary (pri-)miRNA transcripts. These pri-miRNAs are folded into hairpin-like structures that are processed by the microprocessor complex, into a 60-110nt precursor (pre-)miRNA (Figure 1). This pre-miRNA is transported from the

nucleus to the cytoplasm by exportin-5, where the loop region is removed by DICER. The resulting double-stranded RNA molecule is loaded into the RNA-induced silencing complex (RISC), which contains among others one of the four Argonaute (AGO) proteins [42]. One of the two RNA strands is usually degraded while the other strand is retained in the RISC and guides the complex to its target transcripts. Binding of the miRNA-containing RISC to its target genes results in inhibition of translation or mRNA degradation [42].

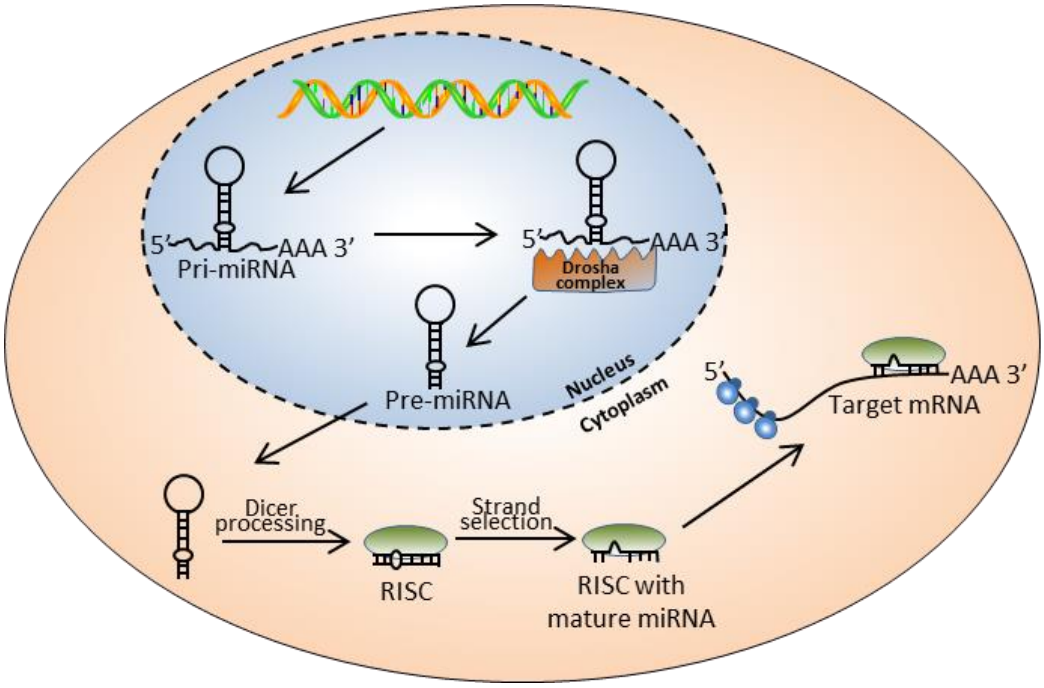


Figure 1. A schematic representation of miRNA biogenesis. MiRNAs are transcribed as long primary (pri-)miRNA transcripts in the nucleus. Based on presence of a stem-loop like structure, the pri-miRNAs are processed by the Drosha-containing microprocessor complex to a precursor (pre-)miRNA. The pre-miRNA is transported to the cytoplasm by exportin-5 protein. In the cytoplasm, the loop is removed by the Dicer complex and one strand of the miRNA duplex becomes the mature miRNA and associates with Argonaute to form the miRNA-induced silencing complex (miRISC). The other strand is usually degraded.

4.1.2 MiRNA target recognition

Most miRNA binding sites are located in the 3'-untranslated regions (3'-UTR) of protein coding gene transcripts. Beside the 3'-UTR, miRNA binding sites can also be present in 5'-UTR and the coding regions of protein coding transcripts, but the impact of this type of interactions on gene regulation has not been well established yet [43]. Target recognition is based on limited homology of the miRNA sequence to the binding site region on the target transcript. In case of canonical binding, the binding sites of transcripts show a perfect complementarity to at least nt 2-7 of the miRNAs, which are defined as the seed sequence [44]. It is estimated that about 6-7% of the miRNA binding sites do not perfectly match to the miRNA seed sequences. Such sites contain bulges or single-nucleotide loops in the miRNA seed region and are

sometimes compensated by extensive 3' end interactions of the miRNA. These miRNA-target gene interaction sites are classified as non-canonical binding sites [39,45,46].

The target spectrum of miRNAs depends on their expression levels in a given cell type: low abundant miRNAs target mainly high-affinity canonical sites, whereas high abundant miRNAs may target both canonical and non-canonical binding sites [47]. Other factors that determine the miRNA binding efficiency are target site accessibility and secondary structure of the miRNA-mRNA duplex [48]. The efficiency of miRNA-mediated regulatory effects on its target genes is crucially dependent on the cellular context. All cell type specific target genes compete for binding with the miRNA. These competing targets do not only comprise transcripts from protein coding genes, but also include noncoding RNA transcripts with miRNA binding sites. Abundantly expressed transcripts with multiple high affinity binding sites can sequester miRNAs and prevent their binding to other cellular targets [42]. This process is referred to as competing endogenous (ce)RNA networks. Transcripts containing multiple binding sites for a specific miRNA are referred to as miRNA sponges. It has been shown that overexpression of such transcripts can protect other transcripts from being targeted by the miRNA [49,50].

By inhibiting translation or inducing transcript degradation, miRNAs regulate a wide range of cellular processes, including B-cell development, migration, adhesion, and immunoglobulin class-switching [51]. Pathways such as NF-kB, PI3K/AKT, and BCR signaling, as well as lymphoma-associated oncogenic regulators, are all subjected to miRNA regulation [52].

4.1.3 MiRNA target identification

Several algorithms have been developed to predict miRNA target genes. Commonly used algorithms are TargetScan and MIRANDA [53,54]. Apart from complementarity between miRNA seed sequences and 3'-UTR of targets, factors such as sequence conservation and RNA accessibility are taken into consideration to predict miRNA target genes [55]. A disadvantage of all available prediction algorithms is that they do not consider co-expression of the miRNA and its target genes, and also do not take potential ceRNA networks into consideration. To circumvent these limitations, several experimental approaches to identify miRNA target genes have been developed. Many of these experimental approaches are based on pulldown of Argonaute proteins present in the RISC complex together with the miRNAs and their target gene transcripts. Analysis of the Argonaute-bound RNAs enables a global identification of the cell type specific miRNA targetome [56]. However, this does not allow to pinpoint specific miRNA-target interactions. Several modifications to this experimental approach have been developed to more directly link the target genes to specific

miRNAs [45,57]. A specific and direct interaction of a miRNA with a target transcript can be validated by luciferase reporter assays. Western blot analysis can be subsequently used to determine the effect of miRNA modulation at the protein level [58].

4.2 Long non-coding RNA

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs which are >200nt long and lack functional open reading frames (ORFs). Transcription and splicing of lncRNAs are similar to protein-coding genes, with similar promoter regions and histone marks, including H3K4me3, H3K4me4, and H3K36me3 [59]. In comparison to protein coding genes, lncRNAs are characterized by an on average lower number of exons, shorter exon length, and lower expression levels [60]. LncRNAs are often classified according to the location relative to protein coding genes, e.g. antisense, intergenic, or intragenic [61] (Figure 2). Most lncRNAs are poorly conserved, but may contain a small region with higher sequence conservation across species, such as XIST, MIAT, PVT1, and MALAT [59,62,63]. In general, lncRNAs have a more tissue- and species-specific expression pattern than protein coding transcripts [64].

The complexity of organisms is positively correlated with the size of the non-coding part of their genome but shows no correlation to the number of protein coding genes. This suggests that non-coding RNAs add to the complexity of organisms [65]. LncRNAs show regulatory functions at the epigenetic and transcriptional levels by acting as transcriptional regulators, transcriptional guides, or scaffolds for chromatin modification complex. Moreover, they are also important players at the post-transcriptional level by regulating mRNA splicing, interacting with miRNAs, as well as affecting stability and functionality of proteins [66] (Figure 3). Well established mechanisms of lncRNAs include: (i) modulation of the three dimensional chromatin structure (e.g. Firre) [67], (ii) scaffolding functions for proteins (e.g. MALAT1 and NEAT1) [68-70], (iii) transcriptional gene regulation via interaction with DNA and/or proteins including epigenetic regulators (e.g. HOTAIR) [71] and transcriptional (co)factors (e.g. lincRNA-p21 and GAS5) [72-74], and (iv) post-transcriptional regulation affecting the stability of mRNAs or proteins (e.g. PVT1 and GAS5) [75,76].

Up to date, LNCipedia identified 127,802 lncRNA transcripts in human [77], while just a small part of these lncRNAs have been functionally annotated [78]. There is an ongoing debate about the proportion of lncRNAs that is really functional [25]. Nonetheless, lncRNAs were shown to act in almost all biological processes, such as viability, growth, motility, immortality, signaling, and proliferation [79,80]. Recently, a genome-wide knockout screen revealed 51 lncRNAs with negative or positive effects on growth of human cancer cells [81].

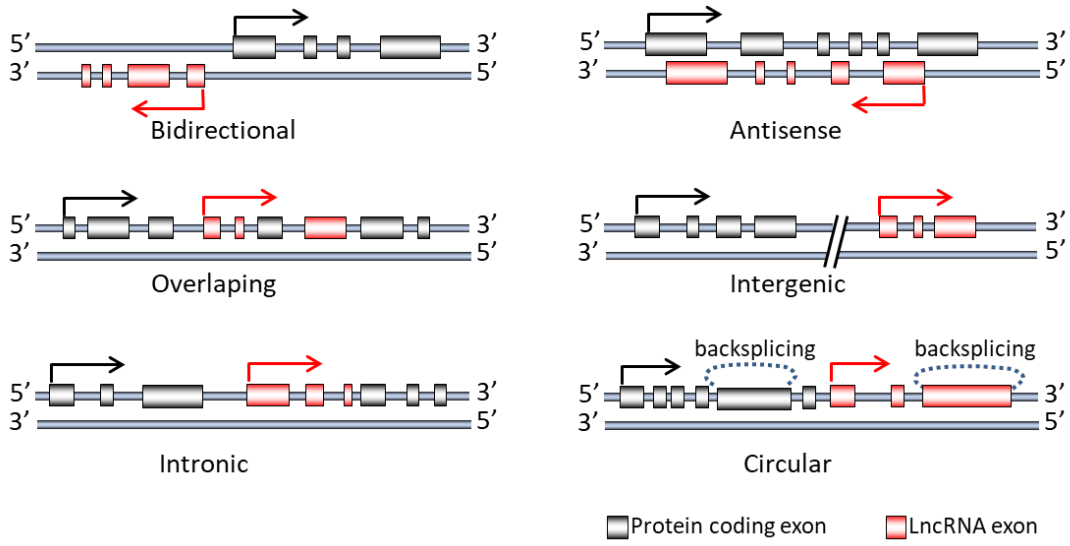


Figure 2. Genomic context of lncRNAs. Subclasses of lncRNAs are categorized based on their location and transcriptional direction relative to protein coding genes. Arrows indicate the transcription start sites.

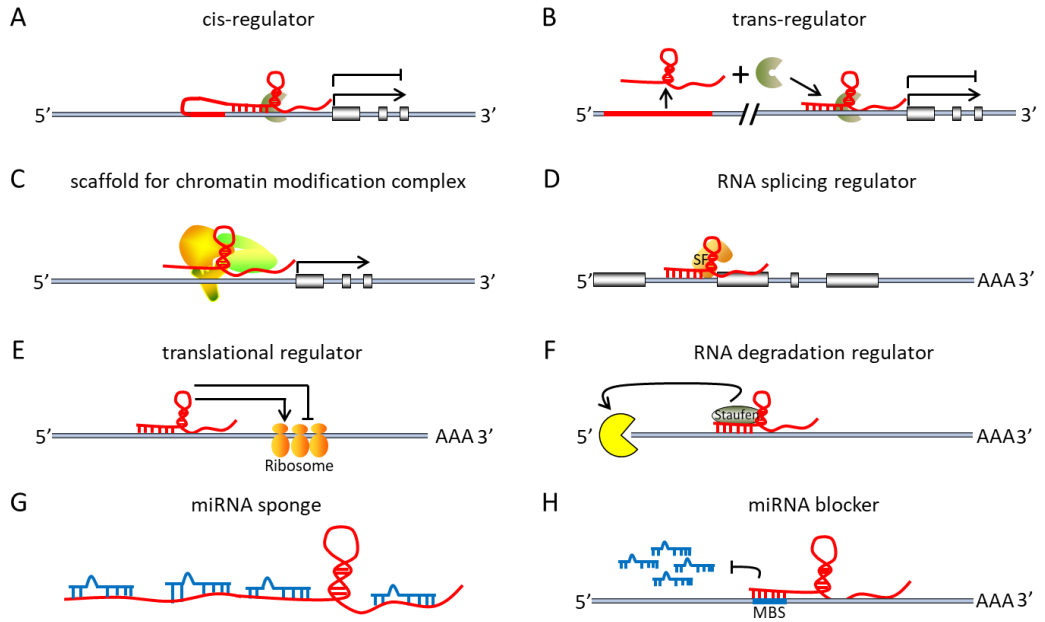


Figure 3. Functional summary of lncRNAs acting at the transcriptional or post-transcriptional level. A) LncRNAs can act as promoters or repressors of transcription in cis. LncRNAs may recruit transcriptional repressors or activators while being transcribed and thus regulate the expression of the nearby protein-coding gene. B) Similar mechanisms have also been described for lncRNAs acting on genes more distant from the lncRNA locus (regulation in trans). C) LncRNAs can act as scaffolds to recruit proteins that form a chromatin modifying complex. At the post-transcriptional level lncRNAs can D) influence alternative splicing, E) promote or inhibit translation or F) control RNA degradation by recruiting RNA decay regulators (i.e. Staufen). G) LncRNAs can also directly interact with miRNAs as miRNA sponge or H) indirectly as miRNA blocker. MBS = miRNA binding site.

4.3 Interactions between lncRNAs and miRNAs

There is strong evidence that lncRNAs interact with miRNAs. Upon binding miRNAs can influence functionality of lncRNAs, or vice versa, lncRNAs can influence

functionality of miRNAs. Binding of let-7 to LincRNA-p21 and HOTAIR resulted in decreased lncRNA levels in a HuR-dependent way [82-84]. Targeting of GAS5 transcripts by miR-21 was shown by Argonaute-2 pull down experiments [85]. Targeting of MALAT1 by miR-9 resulted in degradation of MALAT1 transcripts [86]. Examples of lncRNAs acting as miRNA sponges include among others PTENP1 and GAPLINC. PTENP1 protects PTEN transcripts from degradation by sequestering miRNAs that regulate PTEN expression [87-89]. GAPLINC promoted proliferation of gastric cancer cells by acting as a sponge of miR-378 [90]. The relationship between H19 and let-7 is bi-directional: let-7 can trigger H19 degradation while H19 antagonizes let-7 [84]. MiRNAs and lncRNAs can also indirectly affect each other. For example, some lncRNAs compete with miRNAs by masking the miRNA binding sites on other target transcripts. BACE1-antisense transcripts can bind to the open reading frame of the BACE1 transcript to prevent binding of miR-485-5p. This prevents miRNA-mediated downregulation of BACE1 [91].

5. Non-coding RNAs in B-cell lymphomas

5.1 The role of miRNAs in B-cell lymphomas

In the past decades, multiple studies showed deregulated expression of miRNAs in B-cell lymphoma. Differences in miRNA expression were not only observed between B-cell lymphomas and their normal counterparts but also between different subtypes of GC-B cell derived lymphomas, such as BL, DLBCL, FL and HL [92,93]. A group of 24 miRNAs were differentially expressed in 32 cHL cases as compared to reactive lymphadenopathy [94]. In DLBCL cases, 63 miRNAs showed increased levels and 39 miRNAs were decreased compared to normal centroblasts. Moreover, 6 miRNAs were significantly correlated with patient overall survival [95]. For several of these deregulated miRNAs, oncogenic or tumor suppressive roles involving apoptosis, cell cycle, and proliferation have been demonstrated [52,96-102].

The well-known oncogenic miR-17~92 cluster encodes six miRNAs: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92-1 that are processed from one polycistronic transcript called C13orf25 [103]. The C13orf25 locus is amplified in several types of B-cell lymphomas and overexpression of mature miRNAs is a characteristic feature in multiple lymphoma subtypes [104]. Two members of this miRNA cluster, i.e. miR-19 and miR-92, activate the PI3K-AKT pathway by targeting tumor suppressors PTEN and BIM, which promotes lympho-proliferation and malignant transformation [52,103]. Depletion of miR-17~92 cluster inhibited tumor growth of a xenograft mantle cell lymphoma (MCL) mouse model, suggesting it could be a potential candidate for therapeutic target [105].

MiR-155 is overexpressed in most subtypes of B-cell lymphoma [106]. We have previously shown that miR-155 and its host gene the B-cell integration cluster (BIC)

are highly expressed in HL, PMBL, and DLBCL [107]. Ectopic miR-155 expression in the B-lineage of mice (Eμ-miR-155 transgenic mice) induced proliferation of pre-B cells and development of high-grade lymphoma [108]. MiR-155 directly targets HDAC4, a repressor of BCL6, resulting in upregulation of survival- and proliferation-related genes [109].

Expression of the oncogenic miR-21 is strongly increased in various B-cell lymphoma subtypes. DLBCL relevant target genes of miR-21 include the tumor suppressor genes, PTEN and PDCD4 [110,111]. Conditional overexpression of miR-21 in mice resulted in pre-B-cell like malignancies, which regressed completely upon repression of miR-21 [112]. MiR-21 was shown to be transcriptionally activated by the EBV protein EBNA2 and by NF-kB [113].

In most B-cell lymphomas, miR-150 is a tumor suppressor with a decreased expression level as compared to normal B-cells [114]. It directly targeted MYB, FOXP1 and GAB1, which are transcription factors associated with tumor progression and the BCR signaling pathway [115]. MiR-150 also targeted AKT2, a member of oncogenic PI3K-AKT pathway, resulting in releasing of tumor suppressors, i.e. BIM and p53, from repression, in malignant lymphomas [114,116,117].

5.2 The role of miRNAs in Burkitt lymphoma

To identify miRNAs relevant in BL tumorigenesis, several studies determined miRNAs that are deregulated in BL, and in addition focused on MYC-regulated miRNAs in various MYC models. MiRNAs differentially expressed between endemic BL and GC-B cells included amongst others miR-19b-3p, miR-26a-5p, miR-30b-5p, miR-92a-5p, and miR-27b-3p. These miRNAs were shown to target several BL relevant tumor suppressor genes [118]. A 38-miRNA signature could discriminate BL from DLBCL. Some of these miRNAs were shown to regulate or be regulated by two well-known oncogenic transcriptional regulators, NF-KB and MYC [119]. Another profiling study in BL cases compared to DLBCL and follicular lymphoma (FL) cases revealed 22 deregulated miRNAs with 13 of them being MYC-regulated [120]. We previously identified 39 MYC-regulated miRNAs that were differentially expressed between MYC high BL and other lymphoma samples with low MYC levels. Members of the miR-17~92 cluster were MYC-induced and suppressed chromatin regulatory genes and the apoptosis regulator Bim in BL [121], while known tumor suppressors, such as miR-150, were downregulated [29]. In the Eμ-MYC transgenic mouse model, the miR-17~92 cluster was shown to accelerate B-cell lymphomagenesis by deregulating tumor related pathways, i.e. PI3K and BCR signaling [122]. In contrast to other B-cell lymphomas, miR-155 levels were decreased in BL [108,123]. activation-induced cytidine deaminase (AID) was shown to be a relevant target as increased level of AID were required to promote the formation of the BL hallmark

MYC-IG translocations. Thus, repression of miR-155 may facilitate formation of the chromosomal translocation involving the MYC-IG gene loci, and this may contribute to the malignant transformation of BL precursor cells [124]. RNA immunoprecipitation of Argonaute-2 upon miR-155 inhibition in HL cells and ectopic expression of miR-155 in BL revealed 54 miR-155 specific targets, including the tumor suppressor NIAM. Inhibition of NIAM copied the growth promoting effect of miR-155 in B-cell lymphoma [125].

A tumor suppressor role of miR-150 in BL was shown by decreased cell proliferation upon restoring miR-150 in BL cell lines [97]. We have shown that miR-150 is repressed by MYC and that the remaining miR-150 molecules may be sequestered by the MYC-induced endogenous miR-150 sponges, ZDHHC11 and ZDHHC11B. This most likely is a mechanisms used by BL cells to maintain elevated MYB levels and a high proliferation rate [98].

MiR-28 is a germinal center B-cell specific miRNA whose expression is lost in numerous mature B-cell lymphomas, including BL. MiR-28 targets genes that are required for BCR signaling and play pivotal roles in B-cell biology by regulating proliferation and apoptosis. In BL, miR-28 dampens BCR signaling and impairs B-cell proliferation and survival. Ectopic expression of miR-28 in BL xenografts inhibited tumor growth indicating that miR-28 has tumor suppressor activity and might have therapeutic value in BL treatment [96].

5.3 The role of miRNAs in classical Hodgkin lymphoma

In HL, multiple deregulated miRNAs have been identified with important roles in the pathogenesis being elucidated for a subset of them. A miRNA profiling of 250 samples including HL and normal B-cell subsets revealed high expression of miR-16, miR-21, and miR-155 in cHL cells [126]. Gibcus et al. identified the miR-17-92 cluster, miR-16, miR-21, miR-24, and miR-155 as upregulated miRNAs in HL by microarray [127]. By comparing 49 cHL patients and 10 normal lymph nodes, a distinctive signature of 25 miRNAs was identified [128]. MiR-135a was upregulated in cHL and targeted JAK2, which resulted in reduced levels of the anti-apoptotic gene Bcl-xL [129]. A miRNA profiling in isolated HRS cells from 9 cHL tissue samples and normal B cells revealed 15 deregulated miRNAs [130]. Semra et al. identified 13 miRNAs with decreased and 11 miRNAs with increased expression in cHL tissues compared with normal tissues [94]. The highly abundant miR-17/106b miRNA seed family targeted CDKN1A and this resulted in decreased p21 protein levels, further enabled cell cycle progression of cHL [131]. MiR-9 expression was enhanced in HRS cells and targets the plasma cell differentiation gene PRDM1, which might explain the block in differentiation observed in HRS cells [132]. In addition, miR-9 targets cytokine production related genes HuR and DICER1. Inhibition of miR-9 in a xenograft model

of HL increased the levels of HuR and DICER1 and resulted in decreased tumor growth [133]. Hyper methylation of the miR-124a locus correlated with significantly reduced miR-124a expression and was associated with aggressive cHL disease [134].

5.4 LncRNAs in B-cell lymphoma

LncRNA expression profiling studies in mature B-cell malignancies were mainly applied in cHL, DLBCL and CLL [135]. These studies have clearly shown that a substantial number of lncRNAs are deregulated and indicated distinct expression patterns in B-cell lymphomas. Analysis of RNAseq data revealed 2,632 multi-exonic lncRNAs in DLBCL cases, DLBCL cell lines, naïve B-cells, and GC-B cells. Expression of 88% of them was significantly correlated with at least one protein coding gene [136]. A group of 6 lncRNAs was identified to be associated with overall survival and prognosis in DLBCL patients [137]. More recently, a genome-wide screening covering 10,996 lncRNAs identified 230 cell growth related lncRNAs in CLL [138].

A small number of lncRNAs implicated in tumorigenesis have been functionally annotated [135]. MALAT1 promotes proliferation and metastasis in many solid tumors and is involved in regulation of transcription and alternative splicing [139]. In hematologic malignancies including mantle cell lymphoma (MCL) and multiple myeloma (MM) MALAT1 expression is elevated. Knockdown of MALAT1 inhibited cell proliferation and caused cell cycle arrest in DLBCL, MCL, and MM [140-142]. MEG3 and DLEU1/2 were depleted in hematological malignancies. MEG3 led to accumulation of p53 and downregulating of MDM2 which resulted in inhibition of cell proliferation [143,144]. DLEU1/2 enhanced the expression of the neighboring tumor suppressors, i.e. KPNA3, C13ORF1, and RFP2. Moreover, it encodes for the well-known tumor suppressor microRNAs, miR-15a/16 [145,146].

GAS5 is a lncRNA that was first identified to be specifically expressed in growth-arrested cells [147]. Various characteristics of GAS5 are in line with its function in controlling cell growth: (1) GAS5 was shown to induce growth arrest in normal T lymphocytes [148,149]; (2) depletion of GAS5 blocked apoptosis in MCL and T-cell leukemia [150]; (3) GAS5 knockdown increased levels of CDK6, a protein involved in G1/S transition, which promoted cell cycle and proliferation [151,152]; (4) GAS5 downregulates miR-21, a known onco-miRNA in B-cell lymphomas and miR-21 targets GAS5, thus forming a reciprocal feedback loop [85,112]; (5) GAS5 downregulates MYC at the transcriptional level via interaction with the transcription initiation factor 4E [153]. Altogether these studies showed that GAS5 is a potent tumor suppressor in B-cell lymphoma.

LncRNA-p21 (~17 kb upstream of *p21*) was characterized as a p53-responsive

transcript, affecting different p53-mediated processes, inducing apoptosis, cell cycle arrest, and DNA repair [154]. Conditional knockdown of lincRNA-p21 in murine embryonic fibroblasts diminished p21 levels thereby causing checkpoint defects and increased proliferation [155]. Ectopic expression of lincRNA-p21 in a DLBCL cell line caused an increase in p21 and a G1 cell arrest [156].

Besides these examples, many other annotated lncRNAs, e.g. HULC, HOTAIR, and LUNAR1 are shown to be involved in apoptosis, proliferation, or growth. Several studies, convincingly showed their involvement in the pathogenesis of B-cell lymphoma, but the picture is still far from complete [157-159].

5.5 LncRNAs in Burkitt lymphoma

Because BL is a B-cell lymphoma characterized by a high expression of MYC, the P493-6 B-cell model, which contains a conditional tetracycline-repressible MYC allele, has been used to study the role of MYC in defining the lncRNA landscape in BL. Using this B-cell model, 534 [160], 960 [161], and more than 1,200 [30] MYC-regulated lncRNAs have been identified. One of our previous reports demonstrated that both MYC-induced and MYC-repressed lncRNAs were significantly enriched for MYC binding sites, suggesting a direct regulation of these lncRNAs by MYC [30]. Analysis of BL samples and normal GC-B cells revealed 881 deregulated lncRNAs in BL. Of these lncRNAs, MINCR (MYC-induced noncoding RNA) is characterized as a differentially expressed lncRNA that modulates expression of 1,227 MYC-regulated genes. MINCR depletion caused a G0/G1 cell cycle arrest which impaired BL cell cycle progression [161]. In a more recent report, CRISPR interference (CRISPRi) was applied to explore the effect of MYC-regulated lncRNAs in P493-6 cells and the BL cell line RAMOS. As a result, 320 lncRNAs were shown to be essential for cell proliferation or survival [162]. Silencing of DLEU1 inhibited apoptosis and promoted cell proliferation of BL, which indicated DLEU1 may be a tumor suppressor for BL [163]. However, up to date, most of the deregulated lncRNAs in BL have not been functional annotated nor studied in detail.

5.6 LncRNAs in classical Hodgkin lymphoma

The studies focusing on lncRNA profiling in cHL are limited and very little is known about the functions of lncRNAs in cHL development. In a microarray profiling, we identified 475 lncRNAs differentially expressed between cHL and normal GC-B cells. A potential cis-regulatory role was observed for 107 of differentially expressed lncRNAs localizing within a 60-kb region from a protein coding gene. This study provided a strong rationale to investigate the role of differentially expressed lncRNAs in normal B-cell biology and in cHL cells [164,165]. More recently it was shown that lncRNA H19 was overexpressed in HL tissues and cell lines compared to reactive

hyperplasia of lymph nodes. In addition, H19 expression was negatively correlated with overall survival of HL patients. It was shown that increased levels of lncRNA H19 promoted HL development by stimulating proliferation via activation of the AKT pathway [166]. Leucci et al. described targeting of MALAT1, one of the most abundant and conserved lncRNAs, by miR-9 in cHL. MiR-9 triggered degradation of MALAT1 in the nucleus in an AGO2-dependent way via two miR-9 binding sites [86]. One of the consistently observed susceptibility loci for cHL mapped at 8q24 near the MYC /lncRNA PVT1 locus and was shown to predict patient outcome in two independent cohorts [167].

Scope of the thesis

Although it has become evident that noncoding RNAs can contribute to BL and HL pathogenesis by functioning as tumor suppressor or oncogenes, we know very little about their role for most of them. The aim of this thesis was to identify noncoding RNAs that have an effect on cell growth and explore the relevant functions of selected candidates in BL and HL.

In chapter 2, we performed a high throughput miRNA overexpression screen in HL and identified 4 miRNAs that affected HL cell growth. The oncogenic role of miR-21-5p in HL was investigated in more detail. **In chapter 3**, we identified miRNAs differentially expressed between BL cells and normal GC-B cells and studied the underlying mechanism of miR-378a-3p in BL cell growth. **In chapter 4**, we identified 18 BL cell growth-related miRNAs using a high throughput miRNA gain- and loss-of-function screen and further studied the role of miR-26b-5p in regulating BL cell growth. **In chapter 5**, we applied a similar high throughput screening approach to explore the role of 19 MYC-induced lncRNAs in BL cells. **In chapter 6**, we summarize our studies and discuss future perspectives.

References

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